1,008,468

PATENT SPECIFICATION

NO DRAWINGS

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Int. Cl.:—C 07 f

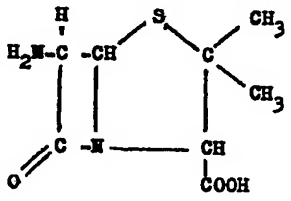
COMPLETE SPECIFICATION

N-Substituted 6-Amino Penicillanic Acids

We, CHEMIE GRUNENTHAL GmbH, a body corporate organised under the laws of Germany, of Postfach 129, Stolberg im Rheinland, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to a process for preparing N - substituted 6 - aminopenicillanic acids.

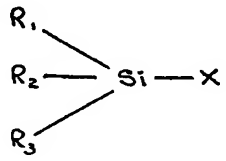
6 - aminopenicillanic acid, has the formula



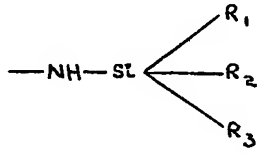
Besides the sulphur containing 5 - membered ring system, 6 - amino - penicillanic acid contains a 4 - membered annular lactam grouping. It is known that this lactam grouping may be split with extreme ease, so that a satisfactory reaction of the skeleton, leading to semi-synthetic penicillins, was not possible until now, for economic as well as technical reasons. A chemical reaction like this would be of outstanding interest because the number of penicillin antibiotics would be enlarged very considerably if a reaction of the 6 - amino - grouping with other compounds, *e.g.* acylation, could be effected. The fundamental difficulty hindering such reactions was, among other obstacles, the fact that dissolving 6 - aminopenicillanic acid in a liquid phase had been impossible without risk of fission of the 4 - membered lactam grouping.

According to the present invention it is now possible to influence the solubility of 6 - amino penicillanic acid type in such a way that it becomes soluble without difficulty in non - proton - active solvents.

The present invention provides a method of preparing N - substituted 6 - aminopenicillanic acids, which comprises reacting 6 - aminopenicillanic acid with silylating agents of the formula



wherein R_1, R_2 and R_3, which may be the same or different, represent alkyl or aryl groups and X represents a hydrogen atom, a halogen atom, the group



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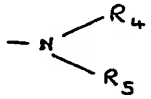


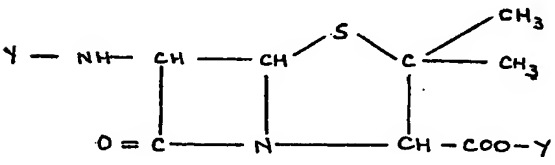
wherein R_4 and R_5, which may be the same or different, represent hydrogen atoms or alkyl groups.

Silylating agents of the formula given above which are especially suitable are those in which X represents a nitrogen containing group and in which the radicals R_1, R_2 and R_3 represent alkyl groups with 1 to 3 carbon atoms, i.e. methyl, ethyl or propyl groups. Besides these aminosilanes or disilazanes, the halogeno silanes are especially useful silylating agents. Especially useful is, for example, a trialkyl chlorosilane which may be

reacted with 6 - aminopenicillanic acid in the presence of ammonia. Other silylating agents known *per se* are the trialkyl silanes. According to the invention, these are applied, especially in the presence of catalysts, e.g. palladium or H_2PtCl_6. In this case hydrogen is liberated.

Preferably, the silylating agents contain trimethylsilyl groups. The product of the silylation reaction with 6 - aminopenicillanic acid has outstanding solubility properties in the usual non-polar solvents, e.g. pure hydrocarbons or petroleum ether. It could not be foreseen that solubility would be enhanced so remarkably, especially when silylating agents which contain lower alkyl groups are used.

One mol of 6 - aminopenicillanic acid reacts when being silylated with two equivalents of the silylating agents, producing compounds of the following formula



I

wherein Y represents trialkyl - silyl, or triaryl silyl groups. It is a matter of particular significance that the 6 - amino grouping adds only one silyl group. One hydrogen atom is consequently left on the amino group, which can be used for a chemical reaction of the 6 - amino group, especially an acylation.

The silylation is effected according to the invention preferably by heating 6 - amino penicillanic acid in the presence of the silylating agent. Usually a non-proton active non-polar solvent may be added. In some instances, reaction may also occur at room temperature; in particular the reaction with trialkyl halogenosilanes may take place at room temperature in the presence of an acid acceptor, e.g. an amine. If silylating is carried out by heating it may be expedient to boil reaction mixture under reflux for several hours. It is especially surprising that amino silanes or disilazanes, may be used for the silylation reaction since they split off ammonia which usually reacts with the β-lactam grouping of 6 - aminopenicillanic acid. Surprisingly it was observed that hexamethyldisilazane at its boiling point (126°C) may be employed for silylation of the 6-aminopenicillanic acid without splitting the β-lactam grouping.

As already mentioned the silyl derivatives of 6 - aminopenicillanic acid of formula I can be used for a chemical reaction at the 6 - amino group, especially an acylation. Accordingly the present invention provides a method for the reaction of the silylated 6 - aminopenicillanic acid. The acylation of the compounds of formula I is done in the usual way, for example, with an acid chloride or an anhydride or with ketenes or with similar acylating agents such as isocyanates or isothiocyanates.

The reaction according to the invention renders possible, for the first time, the preparation of penicillin derivatives which had not previously been made. For instance, it is possible to condense polypeptide moieties with 6 - aminopenicillanic acid in order to make completely new materials available. Fundamentally the acylation especially with acyl chlorides may be carried out at room temperature. Heating is not necessary. As an acid acceptor, an organic base, especially a tertiary amine, may be applied.

In a preferred embodiment of the invention, the reaction of 6 - aminopenicillanic acid with the silylating agent is effected with a considerable excess of the silylating agent. If one silylates 6-aminopenicillanic acid, for instance with hexamethyl disilazane, it may be useful to work with a tenfold excess in weight of the silylating agent. This excess of silylating agent may be removed after reaction with the 6-aminopenicillanic acid, whereby the disilylated compound is obtained.

In a further more especially preferred embodiment of practice of the invention, the following reaction, especially the acylation with an acid chloride for instance, is done without removing the excess of silylating agent. The acylation is done directly in the reaction mixture of the first, (i.e. silylation) step. The excess of silylating agent then acts as solvent. Moreover, when working with an excess of a nitrogen containing silylated agent this may act as an acid acceptor. In this case the additional use of basic agents may be omitted.

After the compounds of formula I have been acylated the silyl groups are removed under conditions which are too mild to open the β-lactam group. This smooth hydrolysis at the end of the reaction sequence is preferably done at low temperatures, for instance room temperature or below. Preferably only that amount of the hydrolysing agent is added which is necessary to remove the silyl groups. The hydrolysis may be made with a usual proton active medium, for instance water or alcohol.

EXPERIMENTAL PART

1) Trimethylsilylation of 6-amino-penicillanic acid

(Preparation of N - trimethylsilyl - 6 - aminopenicillanic acid-trimethylsilylester).

Two grams of 6 - aminopenicillanic acid are refluxed with 20 grams hexamethyldisilazane during 45 mins., whereby 6 - aminopenicillanic acid entered into solution. After cooling down 0.3 grams starting material deposited again which was filtered by suction, so

that 1.7 grams 6 - aminopenicillanic acid was available for the next step, in the form of N-trimethylsilyl - 6 - aminopenicillanic acid trimethylsilylester.

2) Acylation of N-trimethylsilyl-6-aminopenicillanic acid-trimethylsilylester).

(Synthesis of Penicillin G)

To the solution of N-trimethylsilyl-6-aminopenicillanic acid trimethylsilylester in hexamethyldisilazane, prepared according to Example 1, were added 0.9 grams of triethylamine (10% excess) and 1.3 grams of phenylacetic acid chloride at room temperature. The theoretical amount of triethylamine - hydrochloride deposited immediately.

The reaction mixture which warmed up during acylation to about 40°C. was cooled down and then filtered in the absence of moisture. The pure filtrate was concentrated *in vacuo* at a maximum bath temperature of 50°C. and the excess hexamethyldisilazane collected in an acetone-dry ice cooled trap.

As a residue a honey-coloured syrup remained representing penicillin G trimethylsilylester, which was converted into penicillin G by addition of a small amount of water at room temperature.

Yield 90%.

3) Truxillic acid-di-penicillin

1 gram 6-amino-penicillanic acid was refluxed with 10 grams hexamethyldisilazane during 45 min. After cooling down 0.15 grams of unreacted 6 - aminopenicillanic acid could be recovered by filtration. To the pure filtrate 0.5 grams triethylamine was added followed by dropwise addition of 0.65 grams truxillic acid chloride (prepared from raw-truxillic acid) dissolved in a few ml. of CCl_4. The reaction-mixture was kept over night at room temperature. After removing the triethylamine-hydrochloride, the excess hexamethyldisilazane was recovered by distillation *in vacuo*. The silylated final product was converted into truxillic acid-di-penicillin by exposing it to the moisture of the air. Yield almost quantitative.

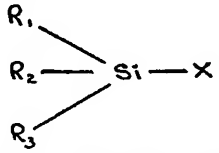
Testing of this preparation for antibiotic acitivity had the following result as compared with the conventional penicillin G-Na:

Staphylococcus test strain	Bacteriostatic dose of penicillin G—Na	Bacteriostatic dose of preparation AR III
SG 511	0.06 γ/ml.	0.5 γ/ml.
V 2370/1	no inhibition at 60 γ/ml.	30 γ/ml.
V 2335/6	no inhibition at 60 γ/ml.	50 γ/ml.

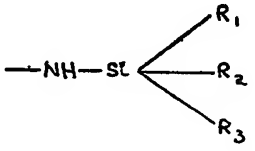
Thus, the preparation is active to staphylococcus strains to which the known penicillin G is inactive.

WHAT WE CLAIM IS:—

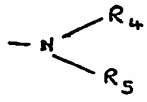
1. A method of preparing N-substituted 6-aminopenicillanic acids, which comprises reacting 6 - aminopenicillanic acid with silylating agents of the formula



wherein R_1, R_2 and R_3, which may be the same or different, represent alkyl or aryl groups and X represents a hydrogen atom, a halogen atom, the group



or the group



wherein R_4 and R_5, which may be the same or different, represent hydrogen atoms or alkyl groups.

2. A method as claimed in Claim 1, wherein the reaction takes place in a non-proton-active and non-polar solvent.

3. A method as claimed in Claim 1 or 2, wherein the silylating agents contain alkyl groups with 1 to 3 carbon atoms.

4. A method as claimed in any of Claims 1 to 3, wherein the reaction with the silylating agent takes place in the absence of proton - active compounds at temperatures between room temperature and the boiling temperature of the silylating agent.

5. A method of preparing 6 - acylamino-

penicillanic acids which comprises reacting 6-aminopenicillanic acid with silylating agents according to Claim 1, dissolving the resultant silylated product in an excess of the silylating agent or in a non-polar solvent, reacting with the desired acylating agent and thereafter splitting off the silicon-containing groups by hydrolysis.

6. A method as claimed in Claim 5, wherein the acylation is carried out using an acylating agent which is an acid halide, acid anhydride, ketene, iso-cyanate or isothiocyanate.

7. A method as claimed in any of Claims 1 to 6, wherein an excess of the silylating agent is used.

8. A method as claimed in Claim 5, wherein the acylation is effected with an acid chloride in the presence of a compound able to fix hydrogen chloride.

9. A method as claimed in any of Claims 5 to 8, wherein the acylation is carried out directly in the reaction mixture of the first stage containing excess silylating agent without isolating the silylated 6-aminopenicillanic acid.

10. A method as claimed in Claim 1, substantially as described with reference to Example 1.

11. A method as claimed in Claim 5, substantially as described with reference to Examples 2 or 3.

12. N-substituted 6-aminopenicillanic acids when obtained by a method as claimed in any of the preceding Claims.

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